The Anthrax Vaccine Program: An Analysis of the CDC's Recommendations for Vaccine Use

The anthrax vaccine was never proved to be safe and effective. It is one cause of Gulf War illnesses, and recent vaccinees report symptoms resembling Gulf War illnesses.

The vaccine's production has been substandard. Without adequate evaluation, the Food and Drug Administration recently approved (retrospectively) significant changes made to the vaccine's composition since 1990. The vaccine's mandatory use for inhalation anthrax is "off-label."

A skewed review of the vaccine literature by the Centers for Disease Control and Prevention (CDC) led to remunerative collaborative research with the army, involving civilian volunteers. Despite acknowledging possible fetal harm, the CDC offered the vaccine to children and pregnant women.

New trends could weaken prelicensure efficacy and safety review of medical products intended for biodefense and avoid manufacturer liability for their use. (Am J Public Health. 2002;92:715–721)

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THIS COMMENTARY WEAVES together 2 stories: the checkered history of the Department of Defense's (DOD's) compulsory Anthrax Vaccine Immunization Program and the role of the Centers for Disease Control and Prevention (CDC) in shoring up the failing vaccine program.

A LICENSED VACCINE BUT AN OFF-LABEL USE

The US Army has considered an ambitious plan to vaccinate all military personnel against biological warfare "threat agents" since at least 1987.[1] Anthrax has been considered to be the number one threat. Anthrax vaccine was the only vaccine planned for biowarfare prophylaxis that had a license, and it was already stockpiled by the military in 1987. The vaccine, however, was not licensed for aerosol exposure[2] (the form of anthrax that would be faced in an attack), since the license was based only on the evidence of an earlier vaccine's efficacy against cutaneous anthrax.[3–6]

A 1995 letter to the vaccine's manufacturer from the director of the army's Medical Chemical and Biological Defense Research Program included a study proposal that acknowledged, "This vaccine is not licensed for aerosol exposure expected in a biological warfare environment."[7] A 1995 report authored by the DOD's anthrax vaccine project manager noted that "protect[ing] service members from aerosol exposure to anthrax can only legally be done if the FDA [Food and Drug Administration] licenses the vaccine for that specific schedule and indication."[8]

These documents recognized that although individual physicians can employ licensed drugs and vaccines for off-label uses, the pros and cons for individual patients must be considered. However, mass vaccination programs, and particularly compulsory programs, bypass the role of the physician in making risk–benefit decisions.[9] Therefore, such programs must use vaccines only for FDA-approved indications.

In 1996, in anticipation of the vaccine's use throughout the armed forces, the anthrax vaccine's manufacturer submitted an investigational new drug application (IND) to the FDA to expand the approved indications for vaccine use.[10] The IND, which had been prepared by the army, allowed the DOD to conduct research to support adding a specific indication for aerosol exposure to the label, changing to an intramuscular injection, and reducing the number of vaccine doses. (The current anthrax vaccine license calls for 6 initial doses over 18 months and then yearly boosters. A soldier embarking on a 20-year military career would thus receive 24 anthrax inoculations before retiring.)

Upon reading *The Cobra Event*, a novel about a biological attack on New York City, President Clinton decided to do something soon about the biological warfare threat.[11] Clinton may not have known that biological weapons, having been used at least since World War I,[12,13] have never injured or killed a single American in battle.[14]

Six months after the IND was filed, but before any supporting data to amend the original license was submitted to the FDA, the assistant secretary of defense for health affairs, Dr Stephen Joseph, asked the acting deputy commissioner of the FDA, Dr Michael Friedman, for a go-ahead to use the vaccine, thus skirting the FDA's normal regulatory procedures for amending a vaccine license.[15] Less than 2 weeks into his new position, Friedman wrote back, "While there is a paucity of data regarding the effectiveness of Anthrax Vaccine for prevention of inhalation anthrax, the current package insert does not preclude this use."[16] However, Friedman's words merely expressed his personal opinion and did not comply with the requirements of the Code of Federal Regulations for amending the vaccine's label; therefore, they provided no legally acceptable justification for the vaccine's off-label use.[17] Anthrax Vaccine Adsorbed is approved by the FDA only for veterinarians and workers handling potentially infected animals or their products and for laboratory workers researching anthrax.[2,3]

In 1997, the DOD finalized the decision to vaccinate all 2.5 million active and reserve military service members, members of the Coast Guard, and certain civilian employees, although no change in the anthrax vaccine label had been approved. At the time, no research had been published that explored the link between anthrax vaccine and Gulf War illnesses, although, in the absence of evidence, expert committees reviewing these illnesses had expressed doubt about a vaccine etiology.[18]

IMMUNIZATIONS PROCEED DESPITE QUESTIONS

On December 15, 1997, the anthrax vaccine program was announced. A few weeks earlier, Secretary of Defense William Cohen had held up a 5-pound bag of sugar on national television and warned that if the bag contained anthrax, it could kill half of Washington, DC. He also promised that 4 preconditions would be met before the program had his final approval.[19] It was later shown that at least 2 of the preconditions were substantially unmet.[20]

Also in December 1997, a team of Russian researchers reported the creation of a genetically engineered anthrax strain that could resist vaccine protection.[21] Later, Ken Alibek, former second-in-command of the Soviet biowarfare program, expressed his concern that additional vaccine-resistant anthrax chimeras had been created.[22]

In March 1998, Secretary Cohen was publicly vaccinated, and mandatory mass vaccinations began. The science to support the program did not exist. There were no published studies documenting the safety or efficacy of this vaccine for any route of exposure in humans,[23] although human studies are required under the Food, Drug and Cosmetic Act. Within weeks, military service members began reporting illnesses following vaccination, while others refused the vaccine. The military leadership responded with court-martials, fines, and less-than-honorable discharges.

In response, an unprecedented 13 congressional hearings explored these issues in depth. In early 2000, the House Committee on Government Reform recommended halting the mandatory program and using the vaccine "only pursuant to FDA regulations governing investigational testing for a new indication." Its report also said, "The subcommittee finds the AVIP [Anthrax Vaccine Immunization Program] a well-intentioned but overwrought response to the threat of anthrax as a biological weapon."[20]

Also responding to congressional concerns, an Institute of Medicine committee, formed to investigate potential causes of Persian Gulf War illnesses, was asked to report on the anthrax vaccine's safety for the DOD. The committee emphasized the lack of evidence for long-term vaccine safety and urged publication of unpublished DOD vaccine studies.[24] Subsequently, DOD investigators published a synopsis of the unpublished studies in the CDC's *Morbidity and Mortality Weekly Report*,[25] glossing over safety concerns by omitting important data from the studies. Having previously reviewed these studies for the General Accounting Office, I noted the omissions in a commentary to ProMED Mail, an Internet mailing list for infectious disease professionals.[26]

CDC OVERSEES ADDITIONAL VACCINE RESEARCH

Three years after the anthrax immunization policy was announced, and after half a million people had already been vaccinated as part of the Anthrax Vaccine Immunization Program, the CDC and its Advisory Committee on Immunization Practices reviewed existing research on anthrax vaccine and made recommendations for vaccine use.[27] Prior to its publication, David Ashford, a coauthor of the recommendations, had been quoted as saying, "We do not have specific information on the efficacy of the existing vaccine for the prevention of inhalational anthrax and we probably never will."[28]

Since the extent of the vaccine's benefit was uncertain, and the dimensions of the biological warfare risk were unknown, the CDC had no easy task, as it attempted to develop appropriate recommendations for vaccine use. However, the CDC recommendations contain inaccuracies and omissions that compound this difficulty.

1. The recommendations state, "The potency and safety of the final [vaccine] product is confirmed according to US FDA regulations." This statement obscures the fact that almost all existing lots of vaccine have been quarantined by the FDA[29] or held up for approval.[30] Furthermore, the FDA did not allow the rebuilt anthrax vaccine manufacturing facility, completed in May 1999, to open until January 2002 because of repeated significant deviations from current good manufacturing practices.[31] The renovated filling suite (where

bulk vaccine is bottled) could not ensure sterility, so the manufacturer has contracted with another pharmaceutical company to package the vaccine.[32] Finally, potency cannot be determined, because the current standard, a guinea pig challenge test, has been shown to be unreliable and irreproducible.[33,34]

2. The quoted 92.5% vaccine efficacy figure was derived from a study of an unlicensed, precursor anthrax vaccine. It is also incorrect, having been calculated by improperly excluding one or more of the vaccinated participants who later developed anthrax.[4,35] Furthermore, it reflected spore counts and strains randomly found in factories, not those likely to be encountered in a biological warfare setting. One might expect to see higher spore concentrations, more virulent anthrax strains, uniform spore sizes, and use of excipients to promote deposition of particles in the terminal alveoli in a bioterrorism event. These features could additionally strain vaccine-induced immunity.[21]

3. The Vaccine Adverse Event Reporting System (VAERS), jointly managed by the CDC and the FDA, collected a very high rate of adverse event reports for anthrax vaccine relative to other vaccines: 1750 reports (from March 1998 to May 2001), or 1 report for every 300 vaccine recipients. Only 54% of these reports showed that there had been a resolution of the reaction when the report was filed.[36]

VAERS is a voluntary, passive reporting system that does not provide actual reaction rates. In the case of military personnel, for whom a vaccine reaction can prevent deployments and career advancement, reporting an adverse reaction can end a career. General Accounting Office testimony before Congress noted that 60% of surveyed air crew members who had had a vaccine reaction did not report it to military medical facilities.[37]

The DOD has now acknowledged that the systemic reaction rate, listed as 0.2% on the package insert, is actually between 5% and 35%.[38] Military vaccine studies have found systemic reaction rates up to 48%.[39] The rate of chronic, unresolved reactions remains unknown, but anecdotally is quite high (29% from an unpublished survey at Dover Air Force Base).[40]

4. The CDC report states, "Analysis of VAERS data documented no pattern of serious adverse events clearly associated with the vaccine." However, in an unpublished analysis of 1660 VAERS reports performed by Thomas D. Williams of the Hartford Courant and by myself, 10% (168) of the reports) note that the vaccine recipient developed at least 2 of the following 3 symptoms: fatigue, muscle or joint pains, and cognitive or emotional impairment. This meets the CDC's own case definition of Gulf War Syndrome.[41] Since Gulf War Syndrome–like illnesses have been reported by vaccine recipients in 3 congressional hearings,[42–44] the CDC or the FDA would be expected to investigate this pattern of illnesses further. However, according to the FDA's Mark Elengold, such a review has not been initiated (written communication, January 16, 2001).

The best sources of information on anthrax vaccine's long-term safety are studies of Gulf War veterans. The CDC report says that 2 CDC studies[41,45] of Gulf War illnesses have "examined a possible association with vaccinations, including anthrax vaccination." The report, however, then admits that for the first study, "the ability of this study to detect a significant difference was limited," and for the second study, "no specific questions were asked about the anthrax vaccine."

Although the 2 cited CDC studies lacked the ability to identify a relationship between anthrax vaccine and Gulf War illnesses, the reports' authors assert that "existing scientific evidence does not support an association between anthrax vaccine and PGW [Persian Gulf War] illnesses." This is not true.

Since 1998, each of the 4 groups reporting on whether specific deployment vaccines[46,47] or anthrax vaccine[48–51] cause symptoms of Gulf War illnesses found a statistically significant, positive association between the two. So has a large Veterans Administration study, in data that have been presented but not yet published.[52] Among nondeployed but vaccinated Gulf War–era veterans from Kansas who received deployment vaccines in preparation for Gulf duty, the rate of Gulf War illness was 3 times higher than in other nondeployed Gulf War–era veterans who did not receive these vaccinations.[46] These nondeployed veterans had no other Gulf War exposures to account for their symptoms.

Making the claim that anthrax vaccination is not related to Gulf War illnesses by citing research that lacked the power to discern a relationship, and ignoring all studies that did show a relationship, does not enhance confidence in the vaccine. It also calls into question the independence of this CDC vaccine review.

The CDC subsequently undertook supervision of a large body of research on anthrax vaccine for the DOD, funded at $23 million, involving several of the CDC recommendation's authors.[53,54] Will similar questions be asked about the scientific integrity of this new research program?

Despite these issues, the CDC recommendations conclude with little support for anthrax vaccination:

> Although groups initially considered for preexposure vaccination for bioterrorism preparedness included emergency first responders, federal responders, medical practitioners, and private citizens, vaccination of these groups is not recommended. Recommendations regarding preexposure vaccination should be based on a calculable risk assessment. At present, the target population for a bioterrorist release of *B. anthracis* cannot be predetermined, and the risk of exposure cannot be calculated. In addition, studies suggest an extremely low risk for exposure related to secondary aerosolization of previously settled *B. anthracis* spores. Because of these factors, preexposure vaccination for the above groups is not recommended. For the military and other select populations or for groups for which a calculable risk can be assessed, preexposure vaccination may be indicated.

The CDC tries to have it both ways. The vaccine is not appropriate for civilians when risk–benefit considerations are taken into account, even for bioterrorism "first responders." But the vaccine is acceptable for military personnel. The CDC's conclusion ignores the fact that *all* military personnel, independent of their specific job or whether they will be deployed to a "high threat" area, are ultimately slated for vaccination. Thus, the decision to vaccinate all service members ignores risk–benefit assessment,

the heart of preventive medicine practice. In acquiescing to the needs of the military, the CDC has established a double standard for the practice of military as opposed to civilian medicine, even in peacetime.

The CDC's recommendations were given wide exposure, being reprinted in the *Journal of the American Medical Association* and the *Journal of Toxicology: Clinical Toxicology*, in addition to *Morbidity and Mortality Weekly Report*. Garnering further attention, free continuing education credits were available for physicians who read the report. Yet, given its failure to evenhandedly review existing information on this vaccine, the report hardly deserves to create the national practice standard to which it aspires.

LEGAL AND ETHICAL CONCERNS

In June 2001, the fourth "slowdown" of the vaccine program was announced, due to limited supplies of vaccine.[55,56] The FDA had not approved release of any vaccine lots for more than a year. The only people then slated for vaccination included potentially exposed research laboratory personnel and special forces troops—the same 2 groups who received the vaccine before the Anthrax Vaccine Immunization Program was initiated. However, vaccine is being held in reserve for the CDC-supervised vaccine trials, which will use civilian volunteers.

Those who refused the vaccine continued to be prosecuted until the Anthrax Vaccine Immunization Program was effectively halted. In May 2001, Capt John Buck, a military physician who refused to receive or administer the vaccine, was court-martialed. Precluded by the military judge from presenting evidence to the jury about the vaccine's IND status, manufacturing problems, or safety and efficacy concerns, he was found guilty.

At his sentencing, Dr Buck said, "I was at the crossroads between the oath of an officer and the oath of a physician. The only way I could have peace about the apparent conflict was to do what I knew to be right as a physician and to stare down the barrel of the gun with the courage of an officer."[57] It is lamentable that physicians have been ordered to abandon good medical practice in aid of a failed vaccine program. Buck, with an exemplary record as a physician, had a pending promotion reversed, was fined $21 000, and was confined to his base for 2 months.

For service members who accept vaccination and subsequently become ill, things are no rosier. Many have been forced to leave the service as a result of their medical problems and have limited ability to earn an income. Moreover, the Feres Doctrine, a body of legal opinion that prevents recovery under the Federal Tort Claims Act [28USC §2674], bars service members from claims against the government for any illness or injury incurred incident to military service.[58]

Anthrax vaccination is only the first vaccine in a planned and funded armed forces–wide program of additional mandatory vaccinations for biological warfare threats, termed the Joint Vaccine Acquisition Program.[59] A military-sponsored National Research Council study released in June 2001 recommended that the army "seek exemptions from some regulatory approval processes to speed up the development of new medical treatments."[60]

Further erosion of existing regulatory protections appears imminent. The FDA has even suggested eliminating human safety testing of medical products designed for chemical and biological warfare prophylaxis, although they are normally required for licensure.[61,62] Although *efficacy* testing of such products in humans may not be feasible, this certainly does not preclude *safety* testing in humans. Animal testing does not ensure human safety. There is no acceptable reason to eliminate human safety testing of any product that the FDA will license for human use.

If a passive FDA continues to allow the DOD to avoid normal scrutiny, as it assumes responsibility for all aspects of development, testing, licensure, manufacture, administration, and adverse event surveillance of future military vaccines and medical products, more military medical disasters almost certainly await us.

CONCLUSIONS

Strong-arm tactics by the DOD, coupled with inadequate oversight and politically driven behavior by CDC and FDA, have resulted in the following problems. The final four points identify needed reforms.

1. The safety and efficacy of the currently used anthrax vaccine have never been established, either for cutaneous or inhalation exposure in humans.

2. FDA standards for use of an IND (experimental) product, which apply equally to civilian and military vaccines, were bypassed because of pressure from the DOD.

3. Anthrax vaccination appears to be one of the causes of Gulf War illnesses.

4. Vaccine manufacture has been substandard. For years, the vaccine manufacturer failed to meet current Good Manufacturing Practices requirements but was allowed to continue production. Over 6 million vaccine doses have been quarantined by the FDA, have failed the army's supplemental testing, or both.

5. Service members have been subjected to a CDC-sanctioned double standard of medical practice in which risk–benefit analysis does not apply.

6. The ability of military physicians to exercise their medical judgment has been suppressed.

7. Ill, recently vaccinated service members, who rely on military medical care and who are barred from filing suit against the government, find themselves reliving the plight of ill Gulf War veterans.

8. Medical professionals, who expect information from the CDC to meet the highest standards, have instead received misrepresentations concerning anthrax vaccine.

9. The CDC is supervising the conduct of safety and efficacy trials of the current vaccine, but its ability to be objective is in question. Furthermore, because the safety issues are unresolved, conducting a large trial of this vaccine in previously unvaccinated individuals is unethical. Retrospective surveillance to assess safety should be performed first on the recent vaccinees, as recommended by the Committee on Government Reform.[20]

10. Medical defense measures for biological warfare, including the Joint Vaccine Acquisition Program, need independent civilian oversight, so that balanced medical decision making can occur, free of the influence of the chain of command.

11. The same regulatory requirements imposed on civilian vaccine and drug manufacturers must be met for military products.

12. Anthrax vaccine should be used *only* in the most dire circumstances. When employed for prophylaxis or treatment of inhalation anthrax, it should be under the conditions required for "off-label" use, including active surveillance for adverse reactions and obtaining free informed consent.

ADDENDUM: THE STORY CONTINUES

Irresponsible decisions by federal agencies have led to over 2 million mandatory anthrax vaccinations in the past four years. Events following September 11 may be leading us further down the slippery vaccine slope.

An October 23, 2001, congressional hearing revealed that changes initiated since 1990 to anthrax vaccine's fermenters and filters were not submitted to the FDA for approval until 2000 and may have led to levels of protective antigen, the vaccine's main immunizing component, one hundred times greater than in the approved preparation.[63] These changes prove that the current anthrax vaccine is not the same vaccine that was licensed in 1970 and should have undergone full safety and efficacy testing to become licensed.

Just days earlier (but after I wrote the article), anthrax was first used offensively in the United States. Its use resulted in 5 deaths, additional infections, and tremendous expenditures and turmoil. The Hart Senate office building remained closed for 3 months pending spore decontamination.

The Ames strain of anthrax was used in the attack. This highly virulent strain was used by the army for vaccine challenge studies[23] but possibly also for other purposes. When used in vaccine experiments, Ames was prepared as a slurry. However, Ames had also been prepared in dry form, in extremely high concentrations, using an additive to promote spore separation and aerosolization. It was this anthrax preparation—made by a highly secret US military process, one for which no defensive use has been given—that was placed in letters to a variety of news media and 2 senators.

This powder's existence, coupled with additional disclosures of attempts to make an anthrax production facility and create a vaccine-resistant strain,[64] strongly suggest that the United States may be violating the Biological and Toxin Weapons Convention. This may help explain the US government's intransigent opposition to strengthening the treaty and the US delegation's walking out of negotiations in July 2001.

US military scientists and contractors seem to have been the only people with access to this powdered, "weaponized" anthrax preparation, although the strain itself was shared with the defense establishments of Canada and the United Kingdom, as well as some universities and private laboratories, including the anthrax vaccine manufacturer. Thus, the source of the attacks is thought to be domestic, someone with access to the military preparation or its secret manufacturing process.

What possible motivation could lead a military scientist to send anthrax in letters that were disguised as those of an Islamic terrorist but that warned that they contained anthrax and that suggested antibiotics? The perpetrator clearly intended to frighten but not to kill. The motive was probably the desire to elevate the status of the biological defense establishment, resulting in increased government funding and attention.[65] After the Clinton presidency's emphasis on the biological weapons threat, the Bush administration's perceived lack of interest may have been seen as a problem in need of a solution. The anthrax vaccine program, for instance, was undergoing a high-level review last summer and might have been minimized or shut down had the attacks not occurred.

Publicly known details of the FBI investigation of the anthrax attacks make it appear half-hearted. The very existence of the powdered preparation, and who had access to it, took months to be reported.

The anthrax attacks gave the CDC an opportunity to study postexposure use of the anthrax vaccine. In this study, the CDC offered the anthrax vaccine to pregnant women and children, although the vaccine was licensed only for those aged 18 to 65 years and was not approved for pregnant females. Prospective vaccinees were offered only 3 doses and received vaccine from a pilot lot that had not been approved for licensed use by the FDA. For these reasons, vaccination was considered experimental and required informed consent.

The consent form said that if study subjects became ill after vaccination, they would not be cared for by the Department of Health and Human Services. The form further noted that preliminary data indicated the vaccine might cause an increased risk of birth defects. Knowing this information, yet offering the vaccine to pregnant women who had received effective prophylaxis with antibiotics, might seem unethical behavior. It could, however, provide the defense department with data they sorely wanted, since so many servicewomen had become pregnant during the anthrax series. The DOD may have hoped the CDC's pregnant cohort would yield evidence of vaccine safety.

After the September attacks, the CDC as a whole received $450 million for bioterrorism preparedness, and the anthrax group received additional funding for their collaborative anthrax vaccine research with the army. ■

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